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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MABRY, JOHN	
ART UNIT	**PAPER NUMBER**
1625	

NOTIFICATION DATE	DELIVERY MODE
12/17/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,733	NAGAI ET AL.	
	Examiner	Art Unit	
	John Mabry, PhD	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner's Response

Applicant's response on 11/08/2007 filed in response to the Office Action dated 6/08/2007 has been received and duly noted. In view of this response, the status of the rejection/objections of record are as follows:

Objection

The amendment to modify the title of the application obviates the objection to the title.

35 USC § 112

The 112-2nd rejection regarding claim 21 has been overcome in view of Applicant's amendment - inserting the phrase "and a pharmaceutical acceptable carrier".

The 112-2nd rejection regarding claims 20 and 22-38 and 42-45 have been overcome in view of Applicant's cancelling the claims.

The 112-1st rejection regarding claims 1-21 has been overcome in view of Applicant's amendment – deleting the phrase "or a hydrate of those".

The 112-1st rejection regarding claims 39-45 has been overcome in view of Applicant's cancelling the claims.

The 112-1st rejection regarding claims 22-45 has been overcome in view of Applicant's cancelling the claims.

Obviousness-Type Double Patenting

The obviousness-type double patenting rejection has not been overcome over Mizui et al. Applicant stated in response to Office Action (dated 6/08/2007) that a properly executed Terminal Disclaimer with respect to Mizui et al will be submitted to overcome rejection.

An action on the merits of claims 1-19 and 21 is contained herein below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substituent" in corresponding claims is a relative term which renders the claim indefinite. The term "substituent" is not defined by the claim, the specification

does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Oxford Dictionary of Chemistry defines the term substituent as an atom or group that replaces another in a substation or an atom or group regarded as having replaced a hydrogen atom in a chemical derivative. The term substituent suggests a limitless number of possibilities of organic compounds. What does Applicant intend by this term? Applicant attempts to provide direction to the term "substituent" on page 52, starting at line 15, which states:

> Given as the substituent in a group "which may have a substituent" used in the specification of the present application is one or more groups selected from:

and then proceeds with a sustained list of possibilities which practically provides no limits to the instant claims (see list on pages 52, line 19 – 57, line 21).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R^7 and R^{21} being O-benzyl, OH, RC(=O)-O-

wherein R=piperazinyl, alkyl, -O-phenyl, -N-alkyl, -NH-phenyl, does not reasonably provide enablement for R^7 and R^{21} being from the list of the following:

wherein R^7 and R^{21}, the same or different, represent

1) a C_2 to C_{22} alkoxy group which may have a substituent,

2) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

3) a C_7 to C_{22} aralkyloxy group which may have a substituent,

4) a 5-membered to 14-membered heteroaralkyloxy group which may have a substituent,

5) RC(=Y)-O-, wherein Y represents an oxygen atom or sulfur atom, and R represents

a)

b) a C_2 to C_{22} alkyl group which have a substituent,

c) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

d) a C_6 to C_{14} aryl group which may have a substituent,

e) a 5-membered to 14-membered heteroaryl group which may have a substituent,

f) a C_7 to C_{22} aralkyl group which may have a substituent,

g) a 5-membered to 14-membered heteroaralkyl group which may have a

substituent,

h) a C_1 to C_{22} alkoxy group which may have a substituent,

i) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

j) a C_6 to C_{14} aryloxy group which may have a substituent,

k) a C_3 to C_{14} cycloalkyl group which may have a substituent,

l) a 3-membered to 14-membered non-aromatic heterocyclic group which may have a substituent or

m) a 5-membered to 14-membered heteroaryloxy group which may have a substituent,

6) $R^{S1}R^{S2}R^{S3}SiO$-, wherein R^{S1}, R^{S2} and R^{S3}, the same or different, represent

a) a C_1 to C_6 alkyl group or

b) a C_6 to C_{14} aryl group,

7) a halogen atom,

8) $R^{N1}R^{N2}N$-R^M-, wherein R^M represents

a) a single bond,

b) -CO-O-,

c) -SO_2-O-,

d) -CS-O- or

e) -CO-NR^{N3}-, wherein R^{N3} represents a hydrogen atom or a C_1 to C_6 alkyl group which may have a substituent, provided that, the leftmost bond in b) to e) is bonded to the nitrogen atom, and

R^{N1} and R^{N2}, the same or different, represent

a) a hydrogen atom,

b) a C_1 to C_{22} alkyl group which may have a substituent,

c) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

d) an aliphatic C_2 to C_{22} acyl group which may have a substituent,

e) an aromatic C_7 to C_{15} acyl group which may have a substituent,

f) a C_6 to C_{14} aryl group which may have a substituent,

g) a 5-membered to 14-membered heteroaryl group which may have a substituent,

h) a C_7 to C_{22} aralkyl group which may have a substituent,

i) a C_1 to C_{22} alkylsulfonyl group which may have a substituent,

j) a C_6 to C_{14} arylsulfonyl group which may have a substituent,

k) a 3-membered to 14-membered non-aromatic heterocyclic group formed by R^{N1} and R^{N2} together in combination with the nitrogen atom to which R^{N1} and R^{N2} are bonded, wherein the 3-membered to 14-membered non-aromatic heterocyclic group may have a substituent,

l) a 5-membered to 14-membered heteroaralkyl group which may have a substituent,

m) a C_3 to C_{14} cycloalkyl group which may have a substituent or

n) a 3-membered to 14-membered non-aromatic heterocyclic group which may have a substituent,

9) $R^{N4}SO_2$-O-, wherein R^{N4} represents

a) a C_1 to C_{22} alkyl group which may have a substituent,

b) a C_6 to C_{14} aryl group which may have a substituent,

c) a C_1 to C_{22} alkoxy group which may have a substituent,

d) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

e) a C_6 to C_{14} aryloxy group which may have a substituent,

f) a 5-membered to 14-membered heteroaryloxy group which may have a substituent,

g) a C_7 to C_{22} aralkyloxy group which may have a substituent or

h) a 5-membered to 14-membered heteroaralkyloxy group which may have a substituent,

10) $(R^{N5}O)_2PO$-O-, wherein R^{N5} represents

a) a C_1 to C_{22} alkyl group which may have a substituent,

b) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

c) a C_6 to C_{14} aryl group which may have a substituent,

d) a 5-membered to 14-membered heteroaryl group which may have a substituent,

e) a C_7 to C_{22} aralkyl group which may have a substituent or

f) a 5-membered to 14-membered heteroaralkyl group which may have a substituent,

11) $(R^{N1}R^{N2}N)_2PO$-O-, wherein R^{N1} and R^{N2} are the same as defined above or

12) $(R^{N1}R^{N2}N)(R^{N5}O)PO$-O-, wherein R^{N1}, R^{N2} and R^{N5} are the same as defined above; or a pharmacologically acceptable salt thereof

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Specification does not provide any support for said variables at R^7 and R^{21} positions. Pages 105-132 of the Specification describe starting

materials and methods for synthesis of compounds wherein R^7 and R^{21} being O-benzyl, OH, RC(=O)-O- wherein R= piperazinyl, alkyl, -O-phenyl, -N-alkyl, -NH-phenyl, does not reasonably describe or list any reagents wherein compounds can be used to synthesis compounds where R^7 and R^{21} being from as listed above.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of highly substituted heterocyclic macrolide compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted heterocyclic macrolide compounds.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I. Pages 105-132 of the Specification describes starting materials and methods for synthesis of compounds wherein R^7 and R^{21} being O-benzyl, OH, RC(=O)-O- wherein R= piperazinyl, alkyl, -O-phenyl, -N-alkyl, -NH-phenyl, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R^7 and R^{21} as listed above. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the moietities and substituents claimed of formula I. Thus, there is no specific direction or guidance regarding said compounds specifically mentioned in Scope.

The specification does not provide any support for the synthesis of compounds, wherein R^7 and R^{21} being the following:

wherein R^7 and R^{21}, the same or different, represent

1) a C_2 to C_{22} alkoxy group which may have a substituent,

2) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

3) a C_7 to C_{22} aralkyloxy group which may have a substituent,

4) a 5-membered to 14-membered heteroaralkyloxy group which may have a substituent,

5) RC(=Y)-O-, wherein Y represents an oxygen atom or sulfur atom, and R represents

a)

b) a C_2 to C_{22} alkyl group which have a substituent,

c) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

d) a C_6 to C_{14} aryl group which may have a substituent,

e) a 5-membered to 14-membered heteroaryl group which may have a substituent,

f) a C_7 to C_{22} aralkyl group which may have a substituent,

g) a 5-membered to 14-membered heteroaralkyl group which may have a

substituent,

h) a C_1 to C_{22} alkoxy group which may have a substituent,

i) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

j) a C_6 to C_{14} aryloxy group which may have a substituent,

k) a C_3 to C_{14} cycloalkyl group which may have a substituent,

l) a 3-membered to 14-membered non-aromatic heterocyclic group which may have a substituent or

m) a 5-membered to 14-membered heteroaryloxy group which may have a substituent,

6) $R^{S1}R^{S2}R^{S3}SiO$-, wherein R^{S1}, R^{S2} and R^{S3}, the same or different, represent

a) a C_1 to C_6 alkyl group or

b) a C_6 to C_{14} aryl group,

7) a halogen atom,

8) $R^{N1}R^{N2}N$-R^{M}-, wherein R^{M} represents

a) a single bond,

b) -CO-O-,

c) -SO_2-O-,

d) -CS-O- or

e) -CO-NR^{N3}-, wherein R^{N3} represents a hydrogen atom or a C_1 to C_6 alkyl group which may have a substituent, provided that, the leftmost bond in b) to e) is bonded to the nitrogen atom, and

R^{N1} and R^{N2}, the same or different, represent

c) a C_1 to C_{22} alkoxy group which may have a substituent,

d) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

e) a C_6 to C_{14} aryloxy group which may have a substituent,

f) a 5-membered to 14-membered heteroaryloxy group which may have a substituent,

g) a C_7 to C_{22} aralkyloxy group which may have a substituent or

h) a 5-membered to 14-membered heteroaralkyloxy group which may have a substituent,

10) $(R^{N5}O)_2PO$-O-, wherein R^{N5} represents

a) a C_1 to C_{22} alkyl group which may have a substituent,

b) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

c) a C_6 to C_{14} aryl group which may have a substituent,

d) a 5-membered to 14-membered heteroaryl group which may have a substituent,

e) a C_7 to C_{22} aralkyl group which may have a substituent or

f) a 5-membered to 14-membered heteroaralkyl group which may have a substituent,

11) $(R^{N1}R^{N2}N)_2PO$-O-, wherein R^{N1} and R^{N2} are the same as defined above or

12) $(R^{N1}R^{N2}N)(R^{N5}O)PO$-O-, wherein R^{N1}, R^{N2} and R^{N5} are the same as defined above; or a pharmacologically acceptable salt thereof

The availability of the starting material that is needed to prepare the invention as claimed is at issue here...As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area,

this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

(5) State of the Prior Art: These compounds are substituted heterocyclic macrolide compounds wherein R^7 and R^{21} being O-benzyl, OH, RC(=O)-O- wherein R=piperazinyl, alkyl, -O-phenyl, -N-alkyl, -NH-phenyl, which are documented in the art. So far as the examiner is aware, no substituted heterocyclic macrolide compounds of general formula I wherein R^7 and R^{21} are described above of any kind have been made or used.

It is not trivial to experimentally interchange any and all of the many groups and substituents that exist. As described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made,

many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Wienheim.

(6) Working Examples: Applicant shows examples 1-3 (on pages 105-132) but no working examples were shown wherein R^7 and R^{21} equals aforementioned moieties and substituents have been made or used of any kind.

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has shown lack of enablement for the groups noted.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

jm

JM

RITA DESAI
PRIMARY EXAMINER

RDesai
12/10/07